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RESEARCH ARTICLE

Predictors of in-hospital mortality among patients with status epilepticus in Lubumbashi, Democratic Republic of the Congo: A retrospective study

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Abstract: Objective: Status Epilepticus (SE) is a condition characterized by an epileptic seizure that persists long enough or recurs at sufficiently short intervals to create a fixed and lasting epileptic condition. The objective of this study was to determine the prevalence and to identify predictors of in-hospital death among SE patients in Lubumbashi, Democratic Republic of the Congo (DRC). **Methods:** We conducted a retrospective study from January 2020 to December 2022. **Results:** Out of 3,006 patients admitted to the neurology department of the University Clinics of Lubumbashi, 97 presented with SE (i.e., a hospital prevalence of 3.23%). The mean age of the patients was 38.38±14.74 years, and men represented 77.3% of the cases. Epileptic patients represented 21.65% of the cases and 66.7% of them were on antiepileptic drugs (AEDs). Seizures were generalized in 72.16% of the patients. Seizures lasted 30 minutes or more in 50.52% of the cases. The most frequent etiologies were strokes, followed by central nervous system (CNS) infections. In-hospital mortality was 24.74% and the predictors of this mortality were CNS infections (adjusted OR = 22.34 [2.69-222.65]; p = 0.0006) and seizures lasting $\geq$ 30 minutes (adjusted OR = 10.98 [2.89-62.70]; p $<$ 0.0001). **Conclusion:** SE is a major neurological emergency requiring early and multidisciplinary management to preserve the vital prognosis because, without treatment, SE causes important neurological complications and even death. The present study found a mortality of 24.74% which was associated with seizure duration of more than 30 minutes as well as with infectious etiologies.

Keywords: Status Epilepticus, mortality, Lubumbashi, DRC

Abbreviations

95% CI: 95% confidence interval
AED: antiepileptic drugs
AOR: adjusted odds ratio
CNS: central nervous system
DRC: Democratic Republic of the Congo
IV: intravenous
SE: status epilepticus
SSA: sub-Saharan Africa

1 Introduction

Status Epilepticus (SE) is a critical condition that requires prompt treatment to minimize the long-term consequences of ongoing seizure activity. In 2015, the International League Against Epilepsy defined SE as "a condition resulting from either failure of mechanisms responsible for seizure arrest or the initiation of mechanisms that lead to abnormally prolonged seizures and may have long-term consequences, including neuronal death, neuronal injury, and alteration of neural networks" [1,2]. Its incidence varies according to the population studied [1]. A variety of etiologies have been described in the literature, including central nervous system infections, brain tumors, stroke, metabolic disorders, etc. [3]. SE is a medical emergency with a higher risk of morbidity and mortality in developing countries than in developed countries [4]. Delayed presentation to the hospital, the difficulty of early implementation of appropriate treatment, the unavailability of certain anti-epileptic drugs, poor clinical and etiological management, particularly of severe and curable causes, and lack of knowledge of pathology all contribute to morbidity and mortality [5].

The objective of this study was to determine the prevalence and to identify predictors of in-hospital death among SE patients in Lubumbashi, Democratic Republic of the Congo (DRC).

2 Materials and methods

2.1 Study design and setting

This was a retrospective cross-sectional study conducted at the Department of Neuropsychiatry of Lubumbashi University Clinics from January 2020 to December 2022. It is the main referral center for all diseases in the southeastern part of the DRC.

2.2 Eligibility criteria and sample size

All patients admitted to the hospital with a diagnosis of status epilepticus by the medical staff, regardless of sex or age, and regardless of etiology, with complete medical records were included in this study. Hence, a total of 97 patients with SE who had been hospitalized during the three-year (2020–2022) study period was collected.

2.3 Data collection

Data were collected using a structured questionnaire which included sociodemographic data (age, sex); etiology of SE including stroke, central nervous system infections, interruption or underdosing of antiepileptic drugs, metabolic disorders, brain tumors, traumatic brain injury, and unknown cause; pre-existing epilepsy; type of epileptic seizures (generalized or partial); duration of epileptic seizures; time from seizure onset to hospital admission; and outcome.

The diagnosis of SE was defined as generalized tonic-clonic seizures: a duration of at least 5 minutes or at least two successive seizures without complete recovery of consciousness between seizures over a period of at least 5 minutes. For partial seizures, a duration of 10 minutes or more was considered. For absence seizures, duration greater than or equal to 15 minutes [2].

2.4 Statistical analysis

For each file, we collected socio-demographic, clinical, and therapeutic features. All analyzes were performed using STATA 16 software. Data for quantitative variables were presented as the mean with its standard deviation as appropriate and for qualitative variables as counts and percentage. Pearson's chi-square test was used to compare proportions. To estimate the probability of death based on factors related, bivariate analysis was performed followed by multiple logistic regression. The adjusted odds ratio (AOR) and its 95% confidence interval (95% CI) were calculated; p-value <0.05 was considered statistically significant.

2.5 Ethical considerations

This study was approved by the Medical Ethical Committee of the University of Lubumbashi (Approval No. UNILU/CEM/126/2022). Due to the retrospective nature of the study, informed consent was not sought from patients as data had been collected from medical records at the hospital. Data analysis was carried out anonymously and in confidence.

3 Results

During the study period, 3,006 patients were seen in the neurology department of the University Clinics of Lubumbashi, including 97 cases of SE (a hospital rate of 3.23%). The mean age of the patients was 38.38 $\pm$ 14.74 years, and men represented 77.3% of the cases. Epileptic patients represented 21.65% of the cases and 66.7% of them were on antiepileptic drugs (AEDs). Seizures were generalized in 72.16% of the patients. Seizures lasted 30 minutes or more in 50.52% of the cases. Brain imaging (CT scan or magnetic resonance imaging) was performed in 86.6% of the patients. The most frequent etiologies were stroke, followed by central nervous systeminfections (Table 1).

Regarding treatment, all patients received first-line treatment with Diazepam at a dose of 0.15 mg/Kg by intravenous (IV) route repeated once if necessary; seizure arrest was recorded in 38.1% (n = 37) of the cases. In the second line of treatment with Phenobarbital at a dose of 15 mg/Kg by IV route; 30.9% (n = 30) of patients showed seizure arrest. After the second line of treatment, 12.4% (n = 12) of the patients developed refractory seizures and were admitted to an intensive care unit, including one patient on Propofol at a dose of 1 mg/Kg by IV route and 11

others on Thiopental at a dose of 100-150 mg by IV route (Figure 1).

The mean length of hospital stay was 6.09 ± 4.17 days. The mean time from the onset of seizures to hospital admission was 5.6 ± 1.9 hours. In-hospital mortality was 24.74% (n = 24). In multivariate analysis, central nervous system (CNS) infections (AOR = 87.99 [1.22-637.02]; p = 0.0304) and seizures lasting ≥ 30 minutes (AOR = 12.52 [2.59-60.48]; p<0.0017) were significantly associated with mortality in patients with SE. Details of the multivariate analysis are shown in Table 2.

Table 1 Etiologies of status epilepticus in 97 patients in Lubumbashi, DRC

Etiologies	Number (n = 97)	Percentage (%)
Stroke		
Haemorrhagic stroke	13	13.4
Sub-arachnoid haemorrhage	6	6.2
Ischaemic stroke	7	7.2
Central nervous system infections		
Toxoplasmosis	3	3.1
Neuromalaria	3	3.1
Cryptococcosis	8	8.2
Meningoencephalitis	8	8.2
Brain tumors	5	5.2
Interruption of antiepileptic drugs	13	13.4
Underdosing of anti-epileptic drugs	2	2.1
Metabolic disorders		
Hypoglycemia	3	3.1
Hyponatremia	2	2.1
Hyperglycemia	4	4.1
Uremic syndrome	2	2.1
Alcohol poisoning	3	3.1
Hydrocarbon poisoning	2	2.1
Traumatic brain injury		
Sub-dural haematoma	3	3.1
Extra-dural haematoma	4	4.1
Cerebral contusion	1	1.0
Unknown	5	5.1

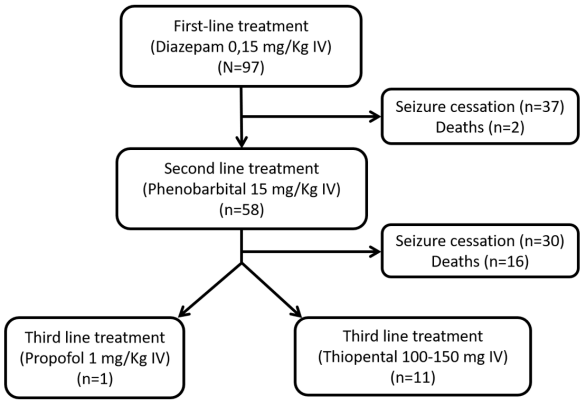

Figure 1 Treatment protocol administered to patients with status epilepticus at their admission in the present study

4 Discussion

In the present study, the SE hospital rate was 3.23%. Compared to epilepsy, the prevalence of SE in sub-Saharan Africa (SSA) is twice as high as in other continents such as Europe, Asia, and North America [6]. A multicenter study by Kariuki et al. [7] in three sites (Agincourt in South Africa, Iganga in Uganda, and Kilifia in Kenya) showed a prevalence of 0.9, 1.4, and 1.1 per 1,000 population respectively. The high rate of SE observed in SSA underscores the need for improved awareness and management of this condition, especially considering the potential for life-threatening complications. The variation in SE prevalence across regions highlights the importance of region-specific approaches to epilepsy management and research. There are several difficulties in assessing the incidence of SE: the quality of prospective data collection,

Table 2 Bivariate and multivariate analysis of factors associated with mortality in patients with status epilepticus in 97 patients in Lubumbashi, DRC

Variable	Total (N = 97)	Death (n = 24), n (%)	Survival (n = 73), n (%)	COR [95% CI]	p-value	AOR [95% CI]	p-value
Age							
$<$ 50 years	78	21 (26.9)	57 (73.1)	1.95 [0.48-11.51]	0.3873	1.69 [0.29-9.90]	0.5598
$\geq$ 50 years	19	3 (15.8)	16 (84.2)	Ref.		Ref.	
Sex							
Male	75	20 (26.7)	55 (73.3)	1.63 [0.46-7.42]	0.5765	6.30 [0.60-66.21]	0.1248
Female	22	4 (18.2)	18 (81.8)	Ref.		Ref.	
Etiology							
Stroke	26	4 (15.4)	22 (84.6)	2.49 [0.23-134.16]	0.6357	7.59 [0.14-425.28]	0.3239
Unknown	5	1 (20.0)	4 (80.0)	3.50 [0.18-69.34]	0.4474	6.64 [0.08-541.69]	0.3993
Central nervous system infections	22	14 (63.6)	8 (36.4)	22.34 [2.69-222.65]	0.0006	87.99 [1.22-637.02]	0.0304
Metabolic disorders	16	2 (12.5)	14 (87.5)	1.96 [0.09-126.28]	1.0000	7.81 [0.13-466.73]	0.3245
Poor compliance with antiepileptic--drugs	15	1 (6.7)	14 (93.3)	Ref.		Ref.	
Traumatic brain injury	8	2 (25.0)	6 (75.0)	4.33 [0.19-294.49]	0.2687	12.99 [0.29-586.94]	0.1873
Brain tumors	5	0 (0.0)	5 (100.0)	0.00 [0.00-117.00]	1.0000	1.00	-
Pre-existing epilepsy							
Yes	21	3 (14.3)	18 (85.7)	Ref.		Ref.	
No	76	21 (27.6)	55 (72.4)	2.27 [0.57-13.28]	0.2633	2.30 [0.09-57.25]	0.6110
Type of epileptic seizures							
Generalized	70	16 (22.9)	54 (77.1)	Ref.		Ref.	
Partial	27	8 (29.6)	19 (70.4)	1.42 [0.45-4.22]	0.6003	1.10 [0.25-4.82]	0.8963
Duration of epileptic seizures							
$<$ 30 minutes	48	3 (6.3)	45 (93.7)	Ref.		Ref.	
$\geq$ 30 minutes	49	21 (42.9)	28 (57.1)	10.98 [2.8962.70]	$<$ 0.0001	12.52 [2.59-60.48]	0.0017
Time from seizure onset to hospital--admission in hours, mean $\pm$ SD		5.5$\pm$2.6	5.6$\pm$1.6		0.9134		0.9948

Notes: AOR: adjusted odds ratio; COR: crude odd ratio; n: number; Ref.: reference; SD: standard deviation; %: percentage; 95% CI: 95% confidence interval.

the problem of common definitions, and the type of populations concerned. It is also necessary to stress the risk of overestimating SE if post-anoxic comas are included in the studies since it is now known that the vast majority of these comas are non-convulsive encephalopathies, even though they are often accompanied by clonus [8].

The mean age of the patients was 38.38$\pm$14.74 years, with men accounting for 77.3% of the cases. An American study by Dham et al. [9] reported a mean age of 38.3$\pm$26.6 years. In Turkey, Ozdilek et al. [10] found a mean age of 32 years. Epileptic patients represented 21.65% of the cases and 66.7% of them were on AEDs. The literature shows a frequency of patients with pre-existing epilepsy varying between 6.94 and 57% [2, 10].

Generalized seizures, such as tonic-clonic seizures, have been found to be the predominant clinical manifestation in many studies of SE, as evidenced by the data collected in the present study (72.16%) and those of other researchers, ranging from 60.5% to 91.8% [7, 11–14]. Several factors may explain the predominance of generalized seizures in SE. Generalized seizures, particularly tonic-clonic seizures, can often be more severe and more prolonged than partial seizures, making them more likely to lead to SE. In addition, generalized seizures may be more likely to spread rapidly through the brain, resulting in generalized epileptic activity. In addition, generalized SE can result from a variety of triggering factors, including a generalized increase in neuronal excitability, disruption of the regulation of inhibitory neurotransmission, ion channel abnormalities, and altered glutamate receptors [15, 16]. These mechanisms can lead to more rapid and complete recruitment of neuronal networks, favoring the generalization of seizures.

The most frequent etiologies in our study were strokes, followed by CNS infections (Table 1). Dham et al. [9] found stroke (7.95%), therapeutic interruption (3.74%), and CNS infections (2.13%) as the main etiologies. Cissé et al. [4], in Guinea, found vascular causes in first place in their adult neurology department, which represented 46.67%, followed by infectious causes (14.4%), tumors (12.2%), and metabolic causes (10%). Although stroke is often found among the etiologies of SE, it is not always the first cause. In Turkey, Ozdilek et al. [10] found therapeutic interruption (31%) followed by systemic infection (23%), brain tumors (19%), central nervous system infection (11%), stroke (8%), and metabolic disorders (4%). A study in Kenya by Newton et al. [3], found that 71% of the cases were of infectious causes (mainly Plasmodium falciparum malaria which accounted for 58%). Infectious etiologies were also found in the study by Reddy et al. [17] in the Republic of South Africa (meningoencephalitis

43% and gastroenteritis 25%). The present study identified strokes as the most common cause of SE, followed by CNS infections. These findings have significant implications for clinical practice, as they emphasize the importance of early recognition and treatment of stroke and CNS infections to prevent SE and its associated complications. Given the resource constraints often present in developing countries, targeted interventions aimed at reducing the burden of these underlying etiologies are warranted.

Our study also showed that treatment for SE predominantly involved the use of diazepam as a first-line treatment and phenobarbital as a second-line treatment. However, the efficacy rates of these treatments were relatively low (38.1% and 30.9%, respectively). This therapeutic protocol had been used by other authors [18–20] and the efficacy of diazepam in first-line treatment was reported to be 56% [20]. However, the efficacy rates of these treatments were modest, indicating the need for more effective therapeutic approaches for SE in resource-limited settings. This underscores the need for improved treatment protocols and access to medications in resource-limited settings. In Turkey, Ozdilek et al. [10] combined diazepam with phenytoin as a first-line treatment with efficacy in arresting seizures in 75% of the cases. Future research should focus on evaluating the efficacy and safety of alternative treatment modalities, including newer antiepileptic drugs in this population.

In this study, in-hospital mortality was 24.74% (n = 24) and CNS infections and seizures lasting $\geq$ 30 minutes were significantly associated with mortality in patients with SE. Status epilepticus is a medical emergency with a high risk of morbidity and mortality in developing countries where the mortality rate varies from 20.2 to 43.33% [4, 11, 14]. Several factors are involved that increase the morbidity and mortality of SE, including delayed presentation to the hospital, ineffective management, and lack of awareness of the condition [5, 19]. In Senegal, patients received after 30 minutes were a factor associated with mortality [21], while in Cameroon, death was associated with meningitis [22]. The prolonged duration of seizures ($>$ 30 minutes) is associated with an increased mortality in SE due to these pathophysiological mechanisms including metabolic resource depletion, failure of cerebral autoregulation, cerebral hypoxia, disseminated intravascular coagulation, and metabolic acidosis, which can damage nerve cells and lead to organ failure, increasing the risk of death. Neuronal damage and excitotoxicity induced by prolonged activation of N-methyl-D aspartate antagonists' receptors can lead to neuron death, especially in vulnerable regions such as the hippocampus and cortex [23]. This neurodegeneration is proportional to the duration of seizures, which underscores the importance of quickly controlling seizures to prevent neuronal damage. Additionally, the reduction in GABAergic inhibition and the persistence of seizures can lead to molecular changes that promote the progression of SE, thereby worsening neuronal damage and increasing the risk of mortality [23, 24]. Therefore, effective seizure management is crucial to reduce seizure duration and improve clinical outcomes in patients with SE.

CNS infections, such as encephalitis, meningitis and brain abscess, can lead to acute inflammation and increased production of pro-inflammatory cytokines. These processes can aggravate neuronal excitotoxicity and favor the onset of prolonged and severe epileptic seizures [25]. In addition, some CNS infections can directly damage brain structures, resulting in permanent neuronal damage and thus increasing the risk of refractory epileptic seizures, which may contribute to increased mortality [26, 27]. In addition, certain CNS infections can alter the blood-brain barrier, favoring the diffusion of stimulants and increasing the risk of prolonged epileptic seizures [28]. Finally, certain CNS infections can induce immune dysfunction, promoting autoimmunity and increasing the risk of refractory epileptic seizures.

As limitations of the study, it should be noted that our study was conducted at the main referral center for all diseases in the southeastern part of the DRC. While this likely ensured a large and diverse study population, it also introduced potential biases. Firstly, our study population may not be fully representative of the entire local population, especially if there are significant differences between those who seek care at the Lubumbashi University Clinics and those who do not. Secondly, as a retrospective cross-sectional study, we were limited by the availability and quality of medical records. We attempted to mitigate this limitation by thoroughly reviewing and validating the data, but there may still be some inaccuracies or missing information. Another limitation of this study was the inability to assess some factors, for example, delayed presentation to the hospital, the difficulty of early implementation of appropriate treatment, the unavailability of certain anti-epileptic drugs, poor clinical, and etiological management, which have reportedly been associated with death. The future study must include these variables. Finally, our study period (January 2020 to December 2022) may not capture the full spectrum of disease prevalence and outcomes, especially considering the impact of the COVID-19 pandemic on healthcare utilization and outcomes. These limitations

and potential biases should be taken into account when interpreting our results.

5 Conclusion

SE is a major neurological emergency requiring early multidisciplinary management to preserve the vital prognosis, because, without treatment, SE causes major neurological complications and death. This study provides valuable insights into the factors associated with mortality in patients with SE. The significant associations of central nervous system infections and prolonged seizure duration with increased mortality emphasize the importance of prompt and effective management strategies. Future research should focus on validating these findings in larger, multi-center studies and exploring potential interventions to improve patient outcomes in SE. Additionally, interventions aimed at improving awareness, treatment protocols, and access to medications are essential for reducing the burden of SE in developing countries.

Data availability

The datasheet used to support the findings of this study is available from the corresponding author (OM) upon request.

Ethics approval and consent to participate

This study was approved by the Medical Ethical Committee of the University of Lubumbashi (Approval No. UNILU/CEM/126/2022). Due to the retrospective nature of the study, informed consent was not sought from patients as data had been collected from medical records at the hospital. Data analysis was carried out anonymously and in confidence.

Competing interests

The authors declare that they have no competing interests.

Author contributions

MB, OM, EKM, and BKB participated in the design of the study. MB, OM, and LND involved in data collection. MB, LND, and OM performed the statistical analysis and drafting of the manuscript with the support of EKM and BKB. All the authors were involved in finalizing the manuscript, read, and approved the final version.

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